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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,226	11/30/2001	Sathyamangalam V. Balasubramanian	19226/2081 (R-5661)	9220

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EXAMINER

WEBER, JON P

ART UNIT PAPER NUMBER

1651

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/000,226

Applicant(s)

BALASUBRAMANIAN ET AL.

Examiner

Jon P Weber, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 16-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4-25,9-9,1
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Status of the Claims

Claims 1-25 have been presented for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-15 in the Paper filed 25 November 2003 is acknowledged. The traversal is on the ground(s) that the respective fields of search between the method and the product are closely related. This is not found persuasive because distinctness and separate search was established in the Office action of 23 October 2003. Evidence for burden is in the separate classification. The product-by-process claims have been combined with the process.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed 25 November 2003. It is suggested that the non-elected claims be canceled in response to this Office action to expedite prosecution.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 25 April 2002, 09 September 2002 and 15 November 2002 have been received and considered.

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Claim Objections

Claims 2-3 are objected to because of the following informalities: "perturabant" is a misspelling. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 09/997,936. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are broader in scope with respect to the proteins stabilized. The conflicting claims are limited to antihemophilic factor (AHF protein), while the instant claims are drawn to all proteins. Otherwise, the claims are identical. In other words, the conflicting claims are a species of the instant genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claim 6 is objected to because of the following informalities: "lysozome" is a misspelling. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 6-9 and 12-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Balasubramanian et al. (Mar 2000).

Balasubramanian et al. (Mar 2000) disclose the partial unfolding of KP6 β (a yeast toxin used as a model protein – see page 344, column 2) which resulted in increase exposure of hydrophobic domains and aggregates, but with the preservation of secondary structure. Liposomes were then interacted with the resulting structured intermediate state, stabilizing the protein against aggregation. These results suggested a general formulation strategy for protein pharmaceuticals, in which partially unfolded structures are stabilized by formulation excipients that act as molecular chaperons to avoid physical instability. Thus, Balasubramanian et al. showed that liposomes bound to partially unfolded structures and prevented the formation of aggregates. Hence, Balasubramanian et al. teach the use of liposomes as stabilizers for protein. Also, Balasubramanian et al. teach and/or suggests a general formulation strategy for any

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protein of interest that forms partially folded structures, e.g., an intermediate state. The first step is to form a "structured" (intermediate) state. This is exemplified by "thermal unfolding, although other methods of unfolding are possible" (page 349, column 2). The second step is to add stabilizing excipients such as liposomes to bind the intermediates. Thus clearly showing the steps of altering the conformation state of the protein and the binding step to a liposome stabilizer of the protein of interest (see especially pages 344 and 349).

Claims 1-3, 6, 8, and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshimoto et al. (1999).

Yoshimoto et al. (1999) disclose that refolding of denatured/oxidized lysozyme is facilitated by a chaperone-like function of liposomes especially SUVs. It is also reported that similar results were obtained with carbonic anhydrase. It is disclosed that since the interaction between denatured proteins and liposomes is primarily hydrophobic, liposomes have the potential to be applied to the refolding of various proteins (page 480). Proteins, like lysozyme, that have disulfide bonds are said to be more difficult to refold. Lysozyme has an early intermediate conformation that is like the molten globule (MG) state that does not have the complete disulfide bonds of the native state. The effect of the SUVs is suggested to be due to a chaperone like activity of binding the hydrophobic partially refolded MG state that must be stabilized to get proper disulfide bond formation. Denaturation/reduced lysozyme was prepared by treatment for at least 5 hr at 25°C with 6M guanidinium chloride and 120 mM DTT. The resulting solution was rapidly diluted into GSH and GSSH containing TRIS buffer in the presence of liposomes to initiate refolding. High yields of active enzyme were obtained.

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Claims 1-2, 12-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (US 5,981,714).

Cheng et al. (US 5,981,714) disclose solubilizing CTFR (cystic fibrosis transmembrane conductance regulator) from its native membrane using detergents (a chemical perturbant) such as CHAPS, n-octyl glucoside, Lubrol, Triton X-100 or Triton X-114. The solubilized CTFR is then stabilized by diluting the detergent concentration and/or adding osmolytes such as glycerol, sugars and amino acids.

Claims 1-3, 7, 12-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Hermann (US 4,965,344).

Hermann (US 4,965,344) discloses denaturing proteins with physical or chemical means (column 3, lines 14-23). Suitable chemical means include guanidinium chloride and urea and other chaotropic agents. A medium containing additives such as sugars, peptides or proteins for enhanced stability is then added and then the denaturing agents are removed by passing the combined solution rapidly through molecular sieves that allow the denaturing agents but not the proteins to sieve. The proteins then refold into a biologically active state.

Claims 1-3, 12-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Jakob et al. (US 5,747,892).

Jakob et al. (US 5,747,892) disclose denaturing proteins, e.g. citrate synthase or Fab fragments, with guanidinium chloride, adding Hsp90 to the denatured enzyme and removing the

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denaturant by dilution to obtain a refolded protein.

Claims 1-3, 7, 12-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bowie et al. (US 5,679,582).

Bowie et al. (US 5,679,582) disclose unfolding a target protein with for example elevated temperatures or addition of chaotropes or denaturants such as guanidinium or detergents. Potentially interactive ligands are added and the extent of folding assessed after ligand binding. Stabilizing ligands increase folding.

Claims 1-3, 12-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Friedman et al. (US 5,935,810).

Friedman et al. (US 5,935,810) disclose adding a denaturing or chaotropic agent such as urea or guanidine-HCl to a recombinantly produced protein. A protein stabilizing agent such as sugar or alcohol is added, and then the denaturant is removed by dilution allowing the protein to refold.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanian et al. (Mar 2000), Yoshimoto et al. (1999), Cheng et al. (US 5,981,714), Hermann (US 4,965,344), Bowie et al. (US 5,679,582) and Friedman et al. (US 5,935,810).

The teachings of Balasubramanian et al. (Mar 2000), Yoshimoto et al. (1999), Cheng et al. (US 5,981,714), Hermann (US 4,965,344), Bowie et al. (US 5,679,582) and Friedman et al. (US 5,935,810) have been discussed above. Balasubramanian et al. (Mar 2000), Yoshimoto et al. (1999), Cheng et al. (US 5,981,714), Hermann (US 4,965,344), Bowie et al. (US 5,679,582) and Friedman et al. (US 5,935,810) lack specific alcohols as chaotropes.

A person of ordinary skill in the art at the time the invention was made would have been motivated to substitute methanol and ethanol for the chaotropes of Cheng et al. (US 5,981,714), Hermann (US 4,965,344), Bowie et al. (US 5,679,582) and Friedman et al. (US 5,935,810) because these alcohols are well known protein denaturing chaotropes. Hence, it would be *prima facie* obvious to substitute these chaotropes for the urea and guanidinium explicitly disclosed in the references. Removing the denaturant by any available means, such as dilution or dialysis are obvious and well known variations.

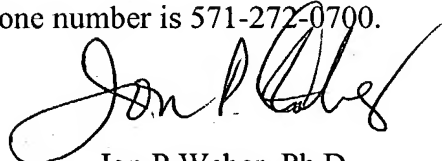
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No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 571-272-0925. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-0700.

A handwritten signature in black ink, appearing to read "Jon P. Weber", with a stylized flourish at the end.

Jon P Weber, Ph.D.
Primary Examiner
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JPW
21 January 2004